

Effects of cigarette smoking and carbon monoxide on nicotine and cotinine metabolism

Objectives: To examine the effects of cigarette smoking on the disposition kinetics of nicotine and cotinine, to determine the effects of cigarette smoking on pathways of nicotine and cotinine metabolism, and to test the hypothesis that carbon monoxide inhibits the metabolism of nicotine.

Study design: Twelve cigarette smokers were studied in three treatment conditions, each lasting 7 days, during which they smoked cigarettes, breathed carbon monoxide to achieve carboxyhemoglobin levels similar to cigarette smoking, or breathed air. In each treatment condition, subjects received a combined infusion of deuterium-labeled nicotine (d_2) and cotinine (d_4), with measurement of disposition kinetics and urine metabolite profile.

Results: Cigarette smoking significantly inhibited the metabolism of nicotine but had no effect on cotinine metabolism. Cigarette smoking markedly induced the *O*-glucuronidation of trans-3'-hydroxycotinine but had no effect on the *N*-glucuronidation of nicotine or cotinine. Carbon monoxide had no effect on nicotine or cotinine kinetics or metabolic profile.

Conclusions: This study confirms previous observations that cigarette smoking inhibits nicotine metabolism but disproves the hypothesis that this effect is due to carbon monoxide. Induction of glucuronidation must be considered in understanding the effects of cigarette smoking on drug metabolism. (Clin Pharmacol Ther 2000;67:653-9.)

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Cigarette smoking is maintained by the effects of nicotine on the smoker, and smokers tend to regulate their daily intake of nicotine from cigarettes.¹ Therefore the rate of nicotine metabolism could influence smoking behavior and the risk of the development of smoking-related diseases. In previous studies we found that the metabolic clearance of nicotine is slower in

smokers compared with that in nonsmokers.^{2,3} This result is in contrast to the well-known effects of cigarette smoking to accelerate the metabolism of many other drugs.⁴

Nicotine is metabolized primarily by oxidative metabolism to cotinine, a reaction believed to be catalyzed predominantly by CYP2A6.⁵⁻⁸ Cotinine is subsequently metabolized, primarily to 3'-hydroxycotinine, also believed to be mediated predominantly by CYP2A6.⁹ Nicotine and cotinine are also conjugated to form *N*-glucuronides, whereas 3'-hydroxycotinine is conjugated to an *O*-glucuronide.⁶ In a previous study we showed that end-product inhibition, that is, cotinine inhibiting the metabolism of nicotine, could not explain the effects of cigarette smoking on nicotine metabolism.¹⁰ Another hypothesis is that carbon monoxide might be inhibiting nicotine metabolism. Carbon monoxide is known to inhibit CYP450 activity in vitro and has been shown to inhibit barbiturate metabolism in rats.^{11,12}

The aims of this study were (1) to examine the effects of cigarette smoking on the disposition kinetics of nicotine and cotinine, (2) to determine the effects of cigarette smoking on pathways of nicotine and cotinine

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metabolism, and (3) to test the hypothesis that carbon monoxide inhibits the metabolism of nicotine. To accomplish the last aim, we developed a novel delivery system to expose subjects to carbon monoxide at levels and in a pattern similar to those experienced during cigarette smoking.

METHODS

Subjects. The subjects were 12 healthy men who were regular cigarette smokers. The subjects (age range, 27 to 47 years) smoked an average of 28 cigarettes per day (range, 18 to 40) and had smoked for an average of 22 years (range, 6 to 33 years). US Federal Trade Commission yields for the usual brands of cigarettes averaged 16.7 mg tar, 1.2 mg nicotine, and 15.5 mg carbon monoxide. Plasma cotinine concentration obtained during outpatient screening before entry into the study averaged 316 ng/mL (range, 184 to 603 ng/mL). The Fagerstrom dependence questionnaire score averaged 7.6 (range, 6 to 10).

The subjects were recruited by advertisement in local newspapers and were financially compensated for participation. The subjects were either unemployed, employed part-time, or self-employed. Five of the subjects consumed alcohol at least weekly (range, 147 to 400 g/week). All subjects denied use of illicit drugs, including marijuana.

The number of subjects was based on a power analysis for repeated-measures ANOVA of nicotine clearance to detect an effect size of 25% assuming a coefficient of variation of 25% with $\alpha = 0.05$ and $\beta = 0.2$.

Experimental protocol. The subjects were studied as inpatients on the General Clinical Research Center at San Francisco General Hospital Medical Center, where they were confined for 21 days. The study was conducted with a within-subject crossover design with three treatments: cigarette smoking, inhalation of carbon monoxide, and inhalation of air. Each treatment was administered for 7 days, and the sequence of treatments was balanced across subjects with 3×3 Latin squares. In the smoking treatment subjects smoked 20 cigarettes per day, one every 45 minutes from 8 AM to 10:15 PM. This treatment could not be blinded. In the air and carbon monoxide conditions, subjects inhaled air or carbon monoxide from 1-L bags once every minute for 10 minutes to simulate the intake of carbon monoxide from cigarette smoking. The inhalation sequence was repeated 20 times per day, on the same schedule as cigarette smoking. The concentration of carbon monoxide in the tank ranged from 1200 to 1500 parts per million (ppm), the concentration calculated to deliver similar doses of carbon monoxide to the smoker

as that delivered by a cigarette. Three subjects inhaled 1200 ppm and 9 subjects inhaled 1500 ppm carbon monoxide. The air and carbon monoxide treatments were blinded to the subjects. Details of the carbon monoxide administration system are provided in the following text.

On the fifth day of each treatment block, subjects were administered a 30-minute infusion of a 50:50 mixture of 3',3'-dideuteronicotine (nicotine- d_2) and 2,4,5,6-tetradeutercotinine (cotinine- d_4). Doses of nicotine and cotinine, expressed as base, were 1.0 $\mu\text{g/kg/min}$ (four subjects), 1.5 $\mu\text{g/kg/min}$ (four subjects), and 2.0 $\mu\text{g/kg/min}$ (four subjects). The dose was the same for a given subject across treatments. Our usual dose of nicotine and cotinine for clearance studies is 2 $\mu\text{g/kg/min}$, but we were concerned because subjects receiving nicotine at times when they are not smoking cigarettes would be expected to be more likely to have nicotine toxicity. However, we found this not to be the case as we gradually increased the dose in successive subjects. Venous blood samples for measurement of nicotine and cotinine levels were collected before, 15, 30, 45, and 60 minutes after, and then 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 32, 44, 56, and 68 hours after the beginning of the infusion. Urine for measurement of nicotine and cotinine and metabolites was collected for 8 hours after initiation of the infusion.

In addition, on day 5 of each treatment block, blood samples were collected every 4 hours over a 24-hour period to determine circadian exposure to nicotine and cotinine in the various treatment conditions. On day 4, subjects also received a test dose of caffeine and on day 6 they received a test dose of chlorzoxazone to explore the effects of cigarette smoking and carbon monoxide on the metabolism of drugs by way of various metabolic pathways. The results of these studies will be reported elsewhere.

Carbon monoxide exposure system. The source of gases were tanks of air or tanks of air with 1200 or 1500 ppm carbon monoxide. The gases were breathed through a mouthpiece that draws the gas from a reservoir (metorologic bag). A one-way valve allowed for inhalation but was shut off after the designated volume (1 L) was inhaled. The valve was controlled by a pneumotachograph that measures flow, coupled to a transducer that signals the valves to close after 1 L of gas flow.

Analysis of nicotine and metabolites in biological fluids. Nicotine and metabolite concentrations were determined by gas chromatography-mass spectrometry. Nicotine, nicotine-3'-3'- d_2 , cotinine, cotinine-2,4,5,6- d_4 , trans-3'-hydroxycotinine, and trans-3'-hydroxycotinine- d_4 were determined by published methods.^{13,14}

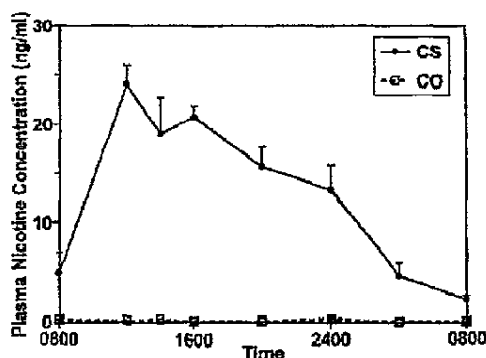


Fig 1. Plasma nicotine concentrations sampled over 24-hour period during cigarette smoking (CS) and carbon monoxide (CO) treatments ($n = 12$; mean \pm SEM). Plasma nicotine levels during air inhalation (not shown for simplicity) were similar to those observed in carbon monoxide inhalation conditions.

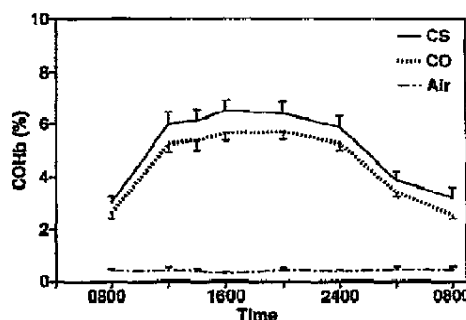


Fig 2. Blood carboxyhemoglobin (COHb) concentrations sampled over 24-hour period during cigarette smoking, carbon monoxide, and air inhalation treatments ($n = 12$; mean \pm SEM).

Glucuronide-conjugated nicotine, cotinine, and trans-3'-hydroxycotinine were measured as the difference in the total concentration before and after hydrolysis by incubation with β -glucuronidase, as described previously.⁶ Enzymatic hydrolysis was performed with 6000 U β -glucuronidase (EC 3.2.1.31, from *Helix Pomita*, Sigma Chemical Co, St Louis, Mo).

Data analysis. Pharmacokinetic parameters were estimated from blood concentration and urinary excretion data with model-independent methods as described previously.¹⁵ Total clearance was computed as follows:

$$CL_{nic} = \frac{\text{Dose (nic-d}_2\text{)}}{AUC \text{ (nic-d}_2\text{)}}$$

and

$$CL_{cot} = \frac{\text{Dose (cot-d}_4\text{)}}{AUC \text{ (cot-d}_4\text{)}}$$

in which CL is clearance and AUC is area under the plasma concentration-time curve extrapolated to infinity. Renal clearances were calculated as follows:

$$\frac{\text{Urinary excretion NIC or COT}}{AUC_{8h}}$$

based on urine collected and the area under the curve for the 8 hours after the infusion. Nonrenal clearance was estimated as total minus renal clearance.

Fractional conversion of nicotine to cotinine (f) was estimated with blood levels of cotinine generated from

infused nicotine and the clearance of cotinine itself, determined by infusion of cotinine, as follows:

$$f = \frac{AUC_{cot-d_2}}{\text{Dose}_{nic-d_2}} \times CL_{cot-d_4}$$

The metabolic clearance of nicotine by way of the cotinine pathway ($CL_{nic \rightarrow cot}$) was computed as $CL_{nic} \times f$.

Urine metabolite data were analyzed based on the urine collection over an 8-hour period after the beginning of the nicotine and cotinine infusion. Urine metabolite concentrations were expressed as a fraction of the total dose of nicotine administered and as a fraction of the total nicotine plus metabolites recovered. The conjugates of nicotine and its metabolites were analyzed as ratios compared with the unconjugated parent compound.

The pharmacokinetic parameters were compared across treatment by repeated-measures ANOVA with a Tukey post test. Where variance differed substantially for different treatments, the data were log-transformed before ANOVA was done.

RESULTS

Nicotine and carbon monoxide exposure in various treatment conditions. Average plasma concentrations of nicotine and blood carboxyhemoglobin in the various treatments are shown in Figs 1 and 2. Plasma cotinine concentrations over a 24-hour period during cigarette smoking (not shown) averaged 270 ng/mL (range,

Table I. Effects of cigarette smoking and carbon monoxide on the disposition kinetics of nicotine (n = 12)

	Cigarette smoking	Carbon monoxide	Air	P Value
Clearance (mL/min)	1232 ± 242*	1376 ± 297	1402 ± 302	<.01 (CO, A>CS)
Nonrenal clearance (mL/min)	1182 ± 236	1281 ± 237	1318 ± 263	.05
Renal clearance (mL/min)	58 ± 36	85 ± 90	84 ± 46	NS
t _{1/2} (min)	154 ± 64	134 ± 30	141 ± 32	.08
V _d (L)	233 ± 84	221 ± 36	244 ± 47	NS
Fractional conversion of nicotine to cotinine	0.67 ± 0.13	0.63 ± 0.10	0.63 ± 0.10	NS
Metabolic clearance by cotinine pathway (mL/min)	832 ± 231	864 ± 222	883 ± 247	NS

Data are presented as mean values ± SD.

t_{1/2}, Half-life; V_d, steady-state volume of distribution; NS, not significant.

*Significant difference compared with other two treatments.

Table II. Effects of cigarette smoking and carbon monoxide on the disposition kinetics of cotinine (n = 12)

	Cigarette smoking	Carbon monoxide	Air	P Value
Clearance (mL/min)	50 ± 18	52 ± 26	46 ± 14	NS
Nonrenal clearance (mL/min)	48 ± 19	49 ± 26	43 ± 14	NS
Renal clearance (mL/min)	3.0 ± 1.2	4.4 ± 2.8	4.3 ± 1.9	NS
t _{1/2} (min)	1016 ± 1110	991 ± 376	1129 ± 312	.08
V _d (L)	62.8 ± 12.3	64.2 ± 10.3	70.0 ± 11.4	<.05 (A>CS)

Data are presented as mean values ± SD.

Table III. Effects of cigarette smoking and carbon monoxide on urinary recovery of nicotine and metabolites (n = 12)*

	Cigarette smoking (%)	Carbon monoxide (%)	Air (%)	P Value
Nicotine	50 ± 20	50 ± 19	58 ± 17	NS
Nicotine glucuronide	8 ± 5	7 ± 4	7 ± 4	NS
Cotinine	8 ± 3	11 ± 5	10 ± 7	NS
Cotinine glucuronide	4 ± 2	3 ± 3	3 ± 2	NS
3'-Hydroxycotinine	8 ± 17	5 ± 3	4 ± 3	NS
3'-Hydroxycotinine glucuronide	5 ± 7†	1 ± 1	1 ± 1	<.005
Nicotine-N-oxide	17 ± 12	24 ± 22	16 ± 8	NS

Data are presented as mean ± SD.

*Based on excretion of nicotine-d₃ and metabolites as a percentage of total recovery in 8-hour urine.

†Significant difference from other treatments; analysis based on log-transformed data.

141 to 362 ng/mL). The carboxyhemoglobin levels were similar in the cigarette smoking and carbon monoxide inhalation conditions (Fig 2). The peak carboxyhemoglobin level averaged 6.7% (range, 4.5% to 8.6%) during cigarette smoking and 5.9% (range, 4.3% to 7.8%) during carbon monoxide inhalation. The 24-hour average carboxyhemoglobin level was 5.3% during cigarette smoking (range, 3.4% to 6.8%) and 4.6% during carbon monoxide inhalation (range, 3.4% to 6.1%).

Disposition kinetics of nicotine and cotinine. The effects of cigarette smoking and carbon monoxide on

disposition kinetics of nicotine and cotinine are presented in Tables I and II and Fig 3. Cigarette smoking significantly decreased the total and nonrenal clearances of nicotine compared with the air and carbon monoxide conditions. No significant treatment effect on renal clearance of nicotine was observed. The half-life of nicotine tended to be longer ($P = .08$) during cigarette smoking as well. Cigarette smoking had no effect on the clearance of cotinine, renal or nonrenal, or on the fractional conversion of nicotine to cotinine. The volume of distribution of cotinine was significantly lower in the cigarette smoking compared with the air treatment condition.

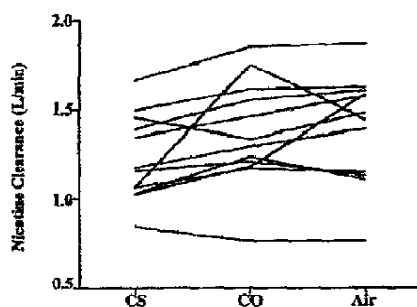


Fig 3. Plasma clearance of nicotine for individual subjects across three treatment conditions. Data on mean and SD values for clearance in each treatment condition are provided in Table I.

Urine metabolite patterns. The values for percentage recovery of nicotine and its metabolites derived from nicotine- d_2 that was infused are shown in Table III. During cigarette smoking the 8-hour urine recovery of trans-3'-hydroxycotinine glucuronide was on average fivefold higher than in the other treatment conditions. No treatment effects were observed for nicotine-*N*-oxide excretion. Cigarette smoking had no effect on *N*-glucuronidation of nicotine and cotinine, as determined either by the ratio of glucuronide to unconjugated nicotine and cotinine or as percentage of total recovery of metabolites (Fig 4 and Table III). Cigarette smoking did substantially increase the ratio of 3'-hydroxycotinine glucuronide/3'-hydroxycotinine, indicating accelerated *O*-glucuronidation.

DISCUSSION

The main findings of our study are as follows:

1. We confirm previous observations that cigarette smoking significantly inhibits the metabolic clearance of nicotine.
2. We present the first evidence that cigarette smoking induces *O*-glucuronidation of 3'-hydroxycotinine, but we find no evidence that cigarette smoking affects *N*-glucuronidation of nicotine and cotinine.
3. We disprove the hypothesis that carbon monoxide inhibits the clearance of nicotine, and we show that carbon monoxide has, in fact, no significant effect on the metabolism of nicotine or cotinine.
4. We find evidence that cigarette smoking decreases the volume of distribution of cotinine.

The design of this study is novel in that it provides a carefully controlled paradigm for studying the effects

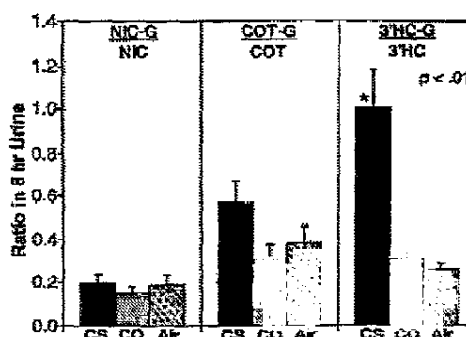


Fig 4. Effects of cigarette smoking and carbon monoxide on glucuronide/precursor ratios based on 8-hour urine collection (mean \pm SEM). Ratios represent metabolites of nicotine- d_2 . NIC, Nicotine; NIC-G, nicotine glucuronide; COT, cotinine; COT-G, cotinine glucuronide; 3'HC, 3'-hydroxycotinine; 3'HC-G, 3'-hydroxycotinine glucuronide.

of cigarette smoking and carbon monoxide alone on drug metabolism. The carbon monoxide exposure system that is described is safe and simulates carbon monoxide exposure from cigarette smoking over a period of several days. One limitation of the study design is that in the no-smoking conditions, lasting 7 to 14 days, there may not have been enough time for all the metabolic effects of cigarette smoking to dissipate. Despite the short no-smoking periods, we did find some substantial differences between the cigarette smoking and no-smoking conditions.

Our study confirms data from two earlier studies that cigarette smoking inhibits nicotine metabolism. Lee et al² found that the clearance of natural nicotine was faster in cigarette smokers after 7 days compared with overnight abstinence from cigarette smoking. Benowitz and Jacob³ showed that the clearance of deuterium-labeled nicotine was faster in nonsmokers compared with that in age- and sex-matched smokers. Thus these two previous studies and this study indicate that something in cigarette smoking is inhibiting nicotine metabolism.

Our data suggest that the main effect of cigarette smoking is to slow the metabolism of nicotine. In a previous study we showed that cotinine was not responsible,¹⁰ and in this study we show that carbon monoxide is not responsible for inhibition of nicotine metabolism. A possibility for this inhibition is the minor alkaloid β -nicotyrine, which has been reported to inhibit nicotine metabolism in mice.¹⁶

Cigarette smoking is well known to accelerate oxidative metabolism of a number of drugs, primarily by inducing the activity of CYP1A1 and 1A2. It is less well known that cigarette smoking can have effects on conjugation of drugs.⁴ In this study we find evidence that cigarette smoking substantially induces *O*-glucuronidation of 3'-hydroxycotinine. However, not all conjugation reactions are accelerated, because we find no evidence of a smoking effect on the *N*-glucuronidation of nicotine and cotinine.

That cigarette smoking may accelerate glucuronide conjugation has been reported previously. Liver microsomes from human smokers are shown to have greater rates of glucuronidation of L-napthol compared with those from nonsmokers.¹⁷ The clearance of oxazepam, which proceeds by way of glucuronide conjugation, is faster in cigarette smokers compared with nonsmokers.¹⁸ Likewise, the glucuronidation of mexilitene and propranolol is accelerated in smokers.^{19,20} Glucuronidation of drugs is catalyzed by UDP-glucuronosyl transferase, of which there are many isozymes with different substrate specificities. Further research is required to identify which UDP-glucuronosyl transferase isozymes are affected by cigarette smoking to anticipate the effects of cigarette smoking on the metabolism of other drugs.

Ours is the first study of which we are aware to test the effects of carbon monoxide on drug metabolism in people. As noted previously, we found no effect of carbon monoxide on the metabolism of nicotine. Based on in vitro and animal studies, it is likely that an effect of carbon monoxide on drug metabolism, if it were to occur, would be seen within 4 or 5 days. Animal studies showing that carbon monoxide inhibits drug metabolism showed effects at substantially higher levels of carbon monoxide than those found in cigarette smokers.¹² Whether carbon monoxide in levels found in smokers has effects on metabolism of other drugs remains to be studied.

The effect of cigarette smoking to decrease the volume of distribution of cotinine was unexpected. One possible explanation for the smoking effect on the distribution volume of cotinine is that smoking produces high background levels of cotinine that could compete for transport into tissues with infused cotinine. However, carbon monoxide had a similar but smaller (and not quite significant) effect on distribution volume compared with that of cigarette smoking, raising the possibility that part of the smoking effect on cotinine distribution is related to an action of carbon monoxide. We are aware of no mechanism by which carbon monoxide would be expected to affect tissue uptake of drugs.

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